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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/553,262	12/20/2005	David Rubinsztein	BJS-620-394	1781

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NIXON & VANDERHYE, PC
901 NORTH GLEBE ROAD, 11TH FLOOR
ARLINGTON, VA 22203

EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
1617	

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07/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/553,262	RUBINSZTEIN ET AL.	
	Examiner	Art Unit	
	Paul Zarek	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 May 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *41-93* is/are pending in the application.

4a) Of the above claim(s) *52-93* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *41-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 October 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/11/2005, 04/06/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 41-93 are currently pending. This is the first Office Action on the merits of the claim(s).

Election/Restrictions

2. Applicant's election without traverse of Group I, drawn to a method of clearing intracellular aggregate-prone proteins, or treating diseases caused by said proteins comprising a stimulating autophagy in the patient, and the species of Huntington's disease and rapamycin macrolides in the reply filed on 05/22/2009 is acknowledged.

3. Claims 41-51 read on the elected species and group. Claims 57-65 are withdrawn as being drawn to a nonelected group. Claims 52-56 and 66-93 are withdrawn as being drawn to a nonelected species.

Priority

4. Applicant's claim for the benefit of a prior-filed international application, PCT/GB04/000690 (filed on 02/24/2004), which claims the benefit of a prior-filed provisional application, 60/462,269 (filed on 04/11/20063), under 35 U.S.C. 119(e) or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. The effective filing date of the instant application is 04/11/2003.

Claim Rejections - 35 USC § 112 (1st paragraph)

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 41-51 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for clearing intracellular aggregate-prone proteins in the treatment of a protein conformational disorder (PCD) comprising stimulation of autophagy, does not reasonably provide enablement for clearing intracellular aggregate-prone proteins in the prophylaxis of a protein conformational disorder (PCD) . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

7. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

a. *The breadth of the claim*: The rejected claims are drawn to a method of clearing intracellular aggregate-prone proteins in the prophylaxis of a PCD. The instant specification defines "prophylaxis" to include treatment as well as prophylaxis (pg 14, lines 32-36).

"Prevent," "prevention," and "prophylaxis" are potent terms implying that the method of prevention, or a prophylactic agent will necessarily prevent PCD in every

patient that receives the treatment at any point following the administration of the prophylactic agent;

b. *Nature of the invention*: The nature of the invention is a method of treating a PCD comprising administration of a stimulator of autophagy;

c. *The state of the prior art*: Ravikumar, et al. (Human Molecular Genetics, 2002, already of record) teach that rapamycin, an inducer of autophagy, decreased protein aggregation, *in vitro* (Fig 4). Ravikumar, et al., suggest that rapamycin, or related analogues, be used for treatments of Huntington's disease (HD) (pg 1113, col 2, para 1, lines 16-20). PCDs, such as HD and Alzheimer's disease, cannot be prevented (Appai-Kubi and Chauduri, pg 6 and InteliHealth, pg 3, respectively);

d. *Level of one of ordinary skill in the art*: Scientists and physicians investigating PCDs would represent an ordinarily skilled artisan;

e. *Level of predictability in the art*: There is little unpredictability in the art with respect of autophagy inducers as therapy for PCDs, and it is generally known that PCDs can be treated, but not prevented;

f. *Amount of direction provided by the inventor*: Applicants discuss the mechanism by which aggregating proteins exert their nefarious effect on the CNS (instant application, pg 1 line 1 through pg 3, line 15). Applicants assert that they have recognized a major route for degradation of aggregate-prone proteins and aggregates (e.g. through autophagy);

g. *Existence of working examples*: Applicants demonstrate the ability of rapamycin to treat HD in *in vivo* models of HD. Applicants have provided no working examples in which rapamycin prevents HD; and,

h. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: The art is clear that PCDs such as HD and Alzheimer's disease cannot be prevented. Applicants have provided no working examples or disclosure indicating that stimulating autophagy would prevent a PCD. Both the Applicants and the art indicate that autophagy-stimulating agents are effective treatments for PCDs, such as HD and Alzheimer's disease. As such, neither the instant specification nor the prior art would enable on of ordinary skill in the art at the time the invention was made to use the claimed invention commensurate in scope with the rejected claims. Undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 112 (2nd paragraph)

8. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

9. Claims 41-51 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejected claims are drawn to a method of clearing "intracellular aggregate-prone proteins." Neither the specification nor the claims define what constitutes an "aggregate-prone protein." It is unclear what protein(s) would be "aggregate-prone." The metes and bounds of the rejected claims are indefinite.

Claim Rejections - 35 USC § 102

10. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

11. Claims 41-51 are rejected under 35 U.S.C. 102(a) as being anticipated by Ravikumar, et al. (above).

12. Claim 41 of the instant application is drawn to a method of clearing intracellular aggregate-prone proteins in the treatment of a PCD comprising stimulating autophagy, wherein said stimulation promotes the clearance of said proteins. Claims 42 and 49-51 limit the PCD. Huntington's disease reads on these claims. Claims 43 limits the stimulation to administration of an autophagy-inducing agent. Claims 44-48 limit the autophagy inducing agent to an mTOR inhibitor, a rapamycin macrolide, rapamycin, a rapamycin analogue, or specific rapamycin analogues, respectively. It is noted that the elected species, rapamycin macrolide and Huntington's disease, read on these claims. Examiner notes the intended result of stimulation of autophagy results in the promotion of clearance of the aggregate-prone proteins. This limitation is the intended result of the claimed method. The intended result of a method is not considered to be a patentably distinguishing feature of an invention. "[A] whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively

recited.'" *Hoffer v. Microsoft Corp.*, 405 F.3d 1326, 1329, 74 USPQ2d 1481, 1483 (Fed. Cir. 2005) (MPEP § 2111.04).

13. Examiner interprets the method of Claim 41 as a method of treating a PCD (i.e. HD) through the stimulation of autophagy activity. The clearing of intracellular aggregate-prone proteins would be considered inherent in any method by which an autophagy-inducing agent is utilized for the treatment of a PCD.

14. Ravikumar, et al., teach that autophagy is the major route of degradation of aggregate-prone proteins associated with HD (pg 1108, col 1, para 3, lines 8-10). They teach that rapamycin inhibits aggregate-containing cells, *in vitro* (pg 1110. para 2, lines 5-8; Fig 4). Ravikumar, et al., suggest that rapamycin, and its related analogues are suitable candidates for treating HD. Therefore, Ravikumar, et al., anticipate all the limitations of the rejected claims.

15. Claims 41-47 and 49-51 rejected under 35 U.S.C. 102(b) as anticipated by Lin, et al. (European Patent Application Publication no. EP 0 778 023 A1, 1997, provided in IDS).

16. Claims 41-47 and 49-51 were discussed above.

17. Lin, et al., teach the use of rapamycin and its analogues for the treatment of neurological disorders, such as Alzheimer's disease, ALS, epilepsy, HD, and Parkinson's disease (pg 8, Claim 4). The number of disease Lin, et al., teach that can be treated by rapamycin or its analogues is sufficiently small in number (five) such that one of ordinary skill in the art could readily envisage the treating the elected species (HD) with the elected agent (rapamycin macrolide). Examiner notes that Lin, et al., do not disclose clearing intracellular aggregate-prone proteins by the taught method. However, given that Lin, et al., disclose treating the same disease (HD) with the same agent (rapamycin), such treatment would inherently clear intracellular aggregate-prone

proteins. Applicants' discovery of the mechanism by which rapamycin treats HD (e.g. through the clearance of intracellular aggregate-prone proteins) is not a patentably distinguishing feature of an invetion. "[T]he discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer." *Atlas Powder Co. v. Ireco Inc.*, 190 F.3d 1342, 1347, 51 USPQ2d 1943, 1947 (Fed. Cir. 1999). Thus the claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. *In re Best*, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977) (MPEP § 2112(I)). Therefore, Lin, et al., anticipate all the limitations of the rejected claims.

Claim Rejections - 35 USC § 103

18. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

19. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

20. Claim 48 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin, et al. (above) in view of the applicant's own admission (see below).

21. Claim 48 was described above.

22. Lin, et al., was described above. Briefly, Lin, et al., disclose a method of treating HD comprising administration of rapamycin or an analogue thereof. Lin, et al., do not disclose the specific rapamycin analogues of Claim 48. However the analogues of Claim 48 are well known rapamycin-derived inhibitors of mTOR (see instant specification, pg 7 line 10 to pg 8 line 1). As such, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use a known analogue of rapamycin for the treatment of HD.

Conclusion

23. Claims 41-51 are rejected.

24. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paul Zarek whose telephone number is (571) 270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/San-ming Hui/
Primary Examiner, Art Unit 1617